Delirium in general medical in-patients in South Africa: development of the 4-question "RACY" tool for simple and effective delirium screening.

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Declaration of originality

This research report is my original work. Neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. None of this work has been published in any format prior to registration for the above-mentioned degree

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Abstract

Objectives: To develop a concise rapid delirium screening instrument to identify general medical in-patients with delirium.

Design: Prospective observational cohort study.

Setting: General medical wards of Groote Schuur Hospital, Cape Town, South Africa.

Participants: 459 medical in-patients older than 16 years.

Outcome measures: Routine delirium testing and barriers to testing. Delirium prevalence and outcomes. Diagnostic accuracy of abbreviated mental test (AMT) and newly developed 4-question "RACY" delirium screening tool.

Results: The median (IQR) age was 45 (31-60) years. Delirium was diagnosed in 20.3% (95%CI: 16.4-24.2) of patients. Delirium was associated with an increased in-patient mortality [OR 3.9 (95%CI: 1.6-9.3), p=0.002] and >7 days hospitalisation [OR: 2.4 (95%CI: 1.2-4.7), p=0.01]. No patient diagnosed with delirium received any formal cognitive testing at the bedside as part of routine care. The newly developed 4-question "RACY' screening tool demonstrated equivalent diagnostic performance to the 10-question AMT, irrespective of the patient's education level, or use of a translator. Using the optimal ROC-selected cut-point of RACY≤2, the sensitivity, specificity, and positive and negative predictive values were 78% (95%CI: 67-86); 85% (95%CI: 80-89); 56% (95%CI: 46-65); and 94% (95%CI: 91-96) respectively.

Conclusions: Although the prevalence of delirium was 20% amongst non-geriatric medical in-patients and associated with poor clinical outcomes, no bedside delirium screening tools were used in routine clinical care. The novel 4-question "RACY" screening tool has the potential to be a simple but effective bedside delirium diagnostic instrument for use in non-geriatric general medical in-patient settings. Its performance was not affected by patient education level and/or the use of a translator.

PART A: Research protocol

The prevalence, incidence & assessment of Delirium using the Abbreviated Mental Test (AMT) in a Tertiary South African hospital with a high HIV prevalence

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Background

Delirium is a mental disorder characterised by acute onset, altered level of consciousness, fluctuating course and disturbances in orientation, memory, thought, perception and behaviour.[1]

A number of prospective studies of the prevalence & incidence of delirium amongst medical inpatients have been carried out. However, studies of delirium show significant heterogeneity, with prevalence & incident rates varying widely across study populations and with differing study design. Prevalence rates of medical inpatients range between 12-31%, with figures as high as 56% in certain elderly hospitalised patients.[2&3] Incidence rates range between 3-25%[2]. The vast majority of these studies looked at elderly patients (Age >65yr), occurred in the setting of developed world tertiary medical centres & in areas of low HIV background prevalence.

It is well-established that delirium is associated with increased mortality (Less robust data of relationship outside of the geriatric population), prolonged hospital length of stay, increased likelihood of placement into a chronic care facility and greater health-care costs[2&3]. A study by Uldall K et al. in AIDS patients showed a significant association with an admission diagnosis of delirium & increased mortality in this patient population[3]. Despite the strength of delirium as a clinical predictor of outcome, it is often under recognised, frequently not sought, and poorly reported in routine clinical practise.

Multiple assessment tools exist for diagnosing delirium & other forms of cognitive impairment in clinical practise such as the Mini-mental State Examination (MMSE) [4] or formal neuropsychiatric cognitive batteries. Unfortunately, within the context of a busy general medical admissions ward where doctors are required to see multiple patients with a number of complex multi-system medical problems in a limited time period many of these cognitive assessment tools are cumbersome & time-consuming. Consequently, they are simply not performed and as a result delirium & dementia are frequently missed.

The Abbreviated Mental Test (AMT) was derived from the modified Roth-Hopkins test in 1972[5]. This simple 10 question, easily administered cognitive screening tool has been validated in the elderly patient population & is widely used in clinical geriatric practise within the United Kingdom. It has been further validated in Chinese population with a predominantly illiterate patient population which more closely resembles our local demographics.[5] The majority of research studies that have looked at the utility of using the AMT in clinical practise have additionally assessed patients whom scored less than 6/10 (Chinese group) & 8/10 (UK groups) on the AMT with the sensitive and specific Confusion Assessment Method (short-version) (CAM) tool developed by Inouye S et al. for the diagnosis of delirium by non-psychiatrists.[6]

South Africa's tertiary medical services admit a wide spectrum of medical problems

reflecting both diseases of the developed and developing world. Additionally, in most parts of the country, tertiary medical services are seeing the ever increasing burden of the HIV/AIDS pandemic, a disease with numerous complex neurological manifestations and predominantly affecting patients between 20-40 years. There are no studies that have recently assessed the prevalence & incidence of delirium & its assessment in tertiary medical centres in South Africa.

Hypotheses

1) In a tertiary medical centre in South Africa, the assessment of delirium in medical inpatients is poor and the condition is frequently under diagnosed. The use of the AMT will provide an easy tool for the rapid assessment of delirium in medical in patients admitted to our tertiary medical centre.
2) The prevalence & incidence of delirium amongst medical in patients in a Tertiary medical centre in South Africa is significantly impacted on by the increasing HIV epidemic. The presence of delirium in these patient correlates with increased mortality, prolonged hospitalisation and increased likelihood of discharge to a secondary care facility.

Aims

1) To determine the prevalence & incidence of delirium in a general medical admission ward in South Africa using the AMT, CAM and MMSE cognitive assessment tools.
2) To analyse the demographics & risk factors associated with delirium in our patient populations as compared with other medical inpatient population reported in the literature.
3) To determine the correlation between the presence of delirium and patient short-term hospital outcomes, including mortality rate, length of hospital admission & necessity for ongoing care in a nursing facility
4) To document the current level of assessment and reporting of delirium/cognitive impairment by doctors working in our tertiary medical wards.
5) To develop a rapid and effective screening tool, derived from the AMT questions, for delirium in general medical in-patients.

Methods

Study setting

Our study population will consist of all medical inpatients admitted to the general medical wards (60 beds) at Groote Schuur Hospital from 14th September to 13th November 2009. Patients will be excluded if they are aphasic, in a coma (GCS ≤ 12/15), admitted to ICU or refuse consent.

Patients will be evaluated within 48 hours of admission to the General Medical ward. Each patient will have a data sheet of clinical and laboratory information completed by the attending medical intern. Subsquently, each patient will be assessed by a second independent junior study doctor, who will first perform the AMT, followed by a review of the inpatient folder documenting whether the presence or absence of delirium has been recorded by the attending medical team. Furthermore, each patient will then independently be assessed by a physician, with knowledge of the DSM-IV criteria for delirium, whom will perform a MMSE together with the Confusion Assesment Method – this combination of tests serving as the gold standard diagnostic method for the presence or absence of delirium. Patients without prevalent delirium will then be screened using the AMT for incident delirium 48-72 hours after the first assessment and then weekly until discharge or diagnosis of delirium.

A data form will be collected for each patient documenting demographic details, the presence or absence of risk factors for delirium, baseline level of patient functioning prior to the current admission. Risk factors that we will document include dementia, depression, visual/hearing impairment, drug/alcohol abuse, focal neurological disease, electrolytes (particularly serum sodium), renal & hepatic function, admission & current medications, HIV status and CD4 count (if known). (See Attached Data form)

Current practice will be reviewed by auditing files for documentation of awareness of risk factors for delirium, the presence or absence of delirium, and the performance of targeted cognitive assessment testing.

Outcomes of patient admissions that will be recorded will include the following: Length of hospital stay, discharge to step down nursing care facility, family care or independent self care & mortality.

Statistical Analysis

Associations with prevalent delirium will be investigated using univariate analysis & assistance will be sought for more detailed analysis from Dr M Badri.

Ethical issues

(i) Ethical approval

Ethical approval for this research study will be sought from the University of Cape Town Health Science Faculty Research Ethics Committee. The continued progress of this project will be subject to the review and approval of the Research Ethics Committee.

(ii) Subject participation and safety

No children will be recruited for this study. All participants will be provided with verbal information and will be asked to give verbal informed consent for all aspects of the study. Verbal consent will be obtained from the family of patients not competent to give consent. Treating doctors will be notified when a diagnosis of delirium or unrecognised

cognitive impairment is made

(iv) Patient confidentiality

Strict subject confidentiality will be maintained throughout participation in the research project. The proposed research proposal conforms to the Helsinki declaration and good clinical practice guidelines.

(v) Conflicts of interest and funding

There are no conflicts of interest

Budgets

There will be no funding required for this study. Study stationary will be supplied by the department of Medicine & Groote Schuur Hospital.

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Part B: Structured literature review

Definition

The word delirium is derived from the Latin word "de" meaning 'off' and "lira" 'track' and thus, literally translated, means 'off track'. Today, delirium is understood to be a complex neuropsychiatric syndrome characterized by a recent onset of fluctuating awareness, impairment of memory and attention, and disorganized thinking due to one or more structural and/or physiological abnormalities directly or indirectly affecting the brain (1). Patients may present with these 'core' neurological abnormalities as well as a variety of others including disturbance in the sleep wake cycle and perceptual abnormalities such as hallucinations (1, 2). In addition to these criteria, and based on psychomotor activity and behavior, delirium can be further classified as hyper-, hypo-active or mixed (2). The diagnosis of delirium remains based entirely on clinical features and diagnostic criteria. The current reference standard criteria for delirium are defined by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) and are listed in Box 1.

Box 1. DSM-IV criteria for delirium (3)

A Disturbance of consciousness (ie reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.
C The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D There is evidence from the history, physical examination, or laboratory findings that:
- the disturbance is caused by the direct physiological consequences of a general medical condition; or
- the symptoms of criteria A and B developed during substance intoxication; or
- medication use is aetiologically related to the disturbance; or
- the symptoms of criteria A and B developed during, or shortly after, a withdrawal syndrome; or
- the delirium has more than one aetiology (eg more than one aetiological general medical condition, a general medical condition plus medication side effect); or
- a clinical presentation of delirium that is suspected to be caused by a general medical condition or substance use but for which there is insufficient evidence to establish a specific aetiology; or
- delirium because of causes not listed in this section (eg sensory deprivation)

Epidemiology and prevalence

Delirium is a common medical disorder diagnosed across a number of different clinical settings. Table 1 shows delirium prevalence and incidence rates stratified by patient setting. Rates are highly variable between elderly care, general medical and surgical in-patient, oncology, emergency and intensive care units as well as in community, residential and nursing homes. Intensive-care and post-operative elderly patients as well as acute medical admissions from elderly chronic care facilities have the highest rates (4). Amongst medical in-patients, a large meta-analysis of 42 studies found that the prevalence of delirium at admission ranged from 10-30% while the incidence of new delirium per admission ranged from 3-29% (5). Of note, however, is the fact that only three of the studies included in this meta-analysis were from a developing country setting, only one involved a non-geriatric cohort (median age <65 years) and none occurred in a high HIV prevalent setting (5). A small study in 137 AIDS patients residing at a chronic care facility found the prevalence of delirium to be 46% at some time during admission (6).

Table 1. Delirium prevalence and incidence in different patient settings

Patient group	Prevalence (%)	Incidence (%)	Reference
Surgery	n/a	15-53	(7-10)
Medical in-patient†	10-31	2-56	(5, 10-13)
AIDS§	46	n/a	(6)
Emergency departments	5-30		(10, 12)
Intensive care units	41-87		(4, 10, 14-16)
Long-term care facilities	40-60	53	(10, 17)

†3 studies from developing country setting; 1 study with median age <60 years
§Prevalence figure of a single study from a developed country HIV/AIDS chronic care facility

Aetiology, pathogenesis and risk factors

Delirium occurs in diverse patient populations secondary to a large number of precipitating factors and aetiology is multifactorial. The development of delirium requires the combination of a vulnerable or predisposed individual and a precipitating event (10). Individuals with greater vulnerability e.g. elderly, institutionalized and/or multiple co-morbidities may require only a small precipitating factor e.g. a single dose of a benzodiazepine in order to present with delirium, while younger, more robust individuals may require multiple insults. Multiple studies have identified predisposing and precipitating factors, and a large number of them are listed below in table 2. Elderly patients, often with multiple comorbidities, are known to have a particular vulnerability to the development of delirium, and globally, form the greatest burden of disease. Geriatricians conduct the majority of delirium research amongst elderly patient cohorts in developed country settings. Consequently, the applicability of many of the factors listed in table 2 to younger medical or intensive care cohorts or to developing country settings with different educational and ethnic profiles as well as unique burdens of communicable and non-communicable diseases is uncertain. More studies from developing countries and younger patient cohorts are required to identify setting-specific patient vulnerabilities and precipitants. This is essential for resource-limited healthcare settings, as it will enable the highest risk patients to be targeted for appropriate preventive and therapeutic interventions.

Table 2. Predisposing and precipitating factors for delirium (1, 2, 10)

Predisposing factor	Precipitating factors
Demographic characteristics	**Drugs**
Age of 65 years or older	Sedative hypnotics
Male sex	Narcotics
Cognitive status	Anticholinergic drugs
Dementia	Treatment with multiple drugs
Depression	Alcohol or drug withdrawal
low education level	**Primary neurological diseases**
Functional status	Stroke, particularly non-dominant hemispheric
Functional dependence	Intracranial bleeding
Immobility	Meningitis or encephalitis
Low level of activity	**Intercurrent illnesses**
History of falls	Infections
Sensory impairment	Iatrogenic complications
Visual impairment	Severe acute illness
Hearing impairment	Hypoxia
Decreased oral intake	Shock
Dehydration	Fever or hypothermia
Malnutrition	Anemia
Drugs	Dehydration
Treatment with multiple psychoactive drugs	Poor nutritional status
Treatment with many drugs	Low serum albumin level
Alcohol abuse	Metabolic derangements (e.g. electrolytes, glucose, acid-base)
Coexisting medical conditions	**Surgery**
Severe illness	Orthopaedic surgery
Multiple coexisting conditions	Cardiac surgery
Chronic renal or hepatic disease	Prolonged cardiopulmonary bypass
History of stroke	Non-cardiac surgery
Neurologic disease	**Environmental**
Metabolic derangements	Admission to an ICU
Fracture or trauma	Use of physical restraints
Terminal illness	Use of bladder catheter
HIV	Use of multiple procedures
	Pain
	Emotional stress
	Prolonged sleep deprivation

Why is delirium important to recognize?

Delirium outcomes and cost

Delirium is a common, serious medical disorder that is associated with significant short, medium and long-term morbidity and mortality and consequent large healthcare cost (5, 6, 10, 26). In-patient mortality rates amongst delirium patients are as high as 76 percent, equivalent to those among patients with acute myocardial infarction or sepsis (10). In-patient delirium is associated with an approximately two-fold increase in discharge and 12-month mortality, a three-to-five-fold increase in post-discharge institutionalization, and an average of five to eight more hospital admission days (1, 10). Additionally, delirium is associated with worse 6 and 12-month cognitive and physical functionality (27, 28). In the USA, incident delirium increases hospital costs by an average of US$2500 per patient so that approximately US$6.9 billion of annual Medicare hospital expenditures can be attributable to delirium (26). In addition, the post-discharge costs of institutionalization, rehabilitative services, and formal or informal nursing care can be substantial (10). The ramifications of delirium on individuals, families and healthcare services are substantive, and the need and use of preventative and therapeutic strategies is essential.

Delirium prevention

The prevention of delirium is considered feasible and cost-effective for elderly patients in developed country settings and tailored multicomponent

interventions now form part of clinical practice guidelines (29). Box 2 shows thirteen of the key recommendations of a multicomponent intervention strategy to prevent delirium from the National Institute of Health and Clinical Excellence (NICE) guidelines (29). High quality evidence for the use of multi-disciplinary and component strategies, such as the Hospital Elder Life Program (HELP), has demonstrated their ability to reduced the development of delirium in hospitalized elderly patients (30). In a prospective cohort of 852 patients >70 years admitted to medical inpatient units, the incidence of delirium was reduced from 15 to 10% using the HELP model (31-33). Modified versions of HELP have also proven beneficial in other developed country settings and this model has now been adopted by 64 sites in 5 countries (30, 33).

Box 2. Thirteen important recommendations to incorporate into a multicomponent intervention to prevent delirium (30)

- Provide a stable care environment with a familiar care team
- Provide tailored multicomponent intervention to persons at risk on hospital admission
- Multicomponent intervention should be delivered by a team trained in delirium prevention
- Address cognitive impairment/disorientation
- Address dehydration and constipation
- Assess for hypoxia
- Look for and treat infection
- Address immobility/limited mobility
- Address pain
- Perform medication review
- Address poor nutrition
- Minimize hearing and vision impairment
- Promote good sleep hygiene

Adapted from the NICE UK delirium guideline (29)

Delirium incidence as a healthcare quality measure

Delirium is considered to be one of the most common preventable adverse events among older people during hospital admission (10, 34, 35). Evidence

suggests that between 30-40% of all cases of delirium are preventable and that many aspects of these multicomponent preventative strategies should form part of routine hospital care (31, 36). Consequently, in the USA, delirium has been included as marker of the quality of care and patient safety by the National Quality Measures Clearinghouse of the Agency for Healthcare Research and Quality (ref) (www.qualitymeasures.ahrq.gov/) (10).

Non-pharmacologic and pharmacologic management of delirium

In addition to preventative strategies, a number of non-pharmacological and pharmacological interventions have been evaluated for the management of delirium. Non-pharmacological approaches involve multicomponent strategies similar to preventative measures and focus on improving orientation and mobility, reducing sensory impairments, and avoiding physical restraints and precipitating drugs e.g. benzodiazepines and antihistamines (30, 37). Studies involving the education of nursing and clinical staff or multicomponent interventions have shown variable success in reducing important patient outcomes such as mortality, length of hospital stay or institutionalization (30, 38-40). If patients require pharmacological therapy for their own safety or the safety of others, haloperidol, or the use of atypical antipsychotics, is commonly recommended (30). Small studies have shown these drugs to reduce the severity of delirium symptoms, but high-quality evidence from randomized control trials demonstrating the ability of antipsychotics or cholinesterase inhibitors to improve patient-important outcomes is lacking (41-43). In addition, neither the atypical antipsychotic medications nor the cholinesterase inhibitors have been

found in clinical trials to offer superior efficacy to haloperidol (44, 45). Interestingly, despite the ongoing use of haloperidol for patient agitation and delirium in routine clinical practice throughout the developing world, there are no high quality studies evaluating its' use in younger delirious patient cohorts. There is an ongoing need to conduct well-design placebo-controlled clinical trials to evaluate the efficacy of antipsychotics and choline esterase inhibitors in delirium so that their ongoing use can be clarified (42, 43).

Delirium under-diagnosis in routine clinical care

Delirium remains under-diagnosed and poorly reported in routine clinical care, despite the large clinical burden and strong association with poor outcomes (10, 46). For instance, in a study where 22 out of 133 consecutively acute medical admissions where diagnosed with delirium, only 1 patient had been reported as delirious by the primary care clinician (47). Healthcare workers have been shown to identify less than fifty percent of delirium cases (47-49). The failure to consider the diagnosis of delirium leads to an inability to target preventative and therapeutic interventions, estimate ongoing care and institutional requirements and prognosticate. Contributing factors to under-recognition include a lack of physician awareness of the clinical consequences of delirium and hence, a failure to consider the diagnosis important, as well as its' fluctuating nature and clinical overlap with dementia (10). These factors considered, the most important obstacles to improve recognition of delirium, especially in over-stretched developing country healthcare settings, remain the challenges of the routine

bedside clinical diagnosis of delirium together with the lack of proven, setting-specific prevention and therapeutic strategies.

Diagnosis of delirium

Categorising delirium bedside instruments

The diagnosis of delirium remains based solely on clinical criteria (3, 10). There are no biomarkers or rapid confirmatory laboratory tests (10). Highly specific diagnostic testing for delirium used today in both research and clinical practice, involves the combination of formal cognitive testing conducted in the context of an in-depth expert assessment evaluating the presence or absence of the clinical criteria consistent with delirium as defined by the DSM-IV (3). Numerous other bedside instruments of varying length and complexity have been developed and validated, largely in elderly patient cohorts, for both delirium screening and high-specificity diagnosis (46, 50). However, despite the availability of numerous validated diagnostic instruments, the under-diagnosis and poor reporting of delirium remains an ongoing problem in routine clinical care (46). Kean and Ryan, and other experts, have suggested that, in both the development and clinical application of bedside delirium instruments, clear tailoring to a specific clinical or research use is required (50, 51). Bedside instruments should be categorization by both their proposed clinical utility i.e. highly specific diagnostic vs. rapid screening tool, and by the level of expertise and training required for their accurate use i.e. expert vs. non-expert (51). Furthermore, given the well-established effects of age and education level on the performance of a number of

cognitive testing tools (52-54), and the greater emphasis on distinguishing between delirium and dementia in elderly patients, a strong argument can be made for population-specific targeting in the use of delirium diagnostic and screening tools.

Table 3A and B outline the most important currently available bedside delirium instruments. Although some instruments offer utility as both diagnostic and screening tools, table 3 stratifies instruments based on the most studied clinical utility and in addition, highlights both their expertise and training requirements and their suitability for use in younger general medical and developing country settings.

Table 3. Bedside delirium instruments utilized in clinical and research settings for:

A. Diagnosis

Bedside delirium instrument	Description	Expert or non-expert tester	Training needed	Overall performance[§]	Comments/suitability to developing country settings
1. ODSM	Based on expert consensus and literature review. Specific criteria as outlined in Box 1	E	Yes	Used as the reference standard for delirium diagnosis in research studies evaluating other diagnostic tools Operationalization can affect inclusivity (50)	Utilisation of criteria requires in-depth clinical understanding. Operationalised criteria often use the Delirium symptom interview together with cognitive screening. Lengthy interview process
2. CAM	Assesses the presence, severity and fluctuation of 9 delirium features: 1(acute onset and fluctuating course) and 2 (inattention) are essential features, and either 3 (disorganized thinking) and 4(altered level of consciousness) is required and determined by expert clinical judgment	E/NE*	Yes	Overall sensitivity and specificity of 94% (95%CI: 91-97) and 89% (95%CI: 85-94) and summary positive and negative likelihood ratios of 9.6 (95%CI: 5.8-16.0) and 0.16 (95%CI: 0.09-0.29) (46, 55) Maybe lower in routine ICU settings (14)	Large evidence base and well validated in number of settings Inadequate training leads to reduction in sensitivity Advised to perform in the context of formal cognitive testing Has been utilized for screening but length and training requirements have significant impact
3. MMSE	30-item brief cognitive testing tool Items test orientation, memory and concentration	NE	No	MMSE<24 sensitivity and specificity of 96% (95%CI: 87-99) and 38% (95%CI: 23-55) and summary positive and negative likelihood ratios of 1.6 (95%CI: 1.2-2.0) and 0.12 (95%CI: 0.04-0.38) (46, 56)	Useful tool to determine the presence of cognitive impairment, especially for dementia screening in elderly populations (50). Recommended use together with other delirium screening tool e.g. CAM (55) Changes in MMSE during hospital admissions useful to detect incident delirium (57) Significantly affected by education, literacy and English language proficiency level (53, 54, 58, 59) Time-consuming in busy clinical environment
4. DRS	10 item observational scale (range 0-32) that rates patients on the characteristic symptoms of delirium	E	Yes	DRS ≥10: Overall sensitivity and specificity of 95% (95%CI: 90-98) and 79% (95%CI: 58-91) summary positive and negative likelihood ratios of 4.3 (95%CI: 2.1-9.1) and 0.07 (95%CI: 0.03-0.13) (46)	Test developed for use by specialist psychiatrist Time-consuming test (>5 mins) limit utility Useful for research reference diagnostic testing
5. DRS-Revised 98	Revised version of the DRS. More comprehensive and separates the scale into 2 sections: 3 diagnostic items for initial rating and a 13-item scale for repeated measures	E	Yes	Overall sensitivity and specificity of 93% (95%CI: 80-98) and 89% (95%CI: 68-97) summary positive and negative likelihood ratios of 8.0 (95%CI: 2.6-25) and 0.08 (95%CI: 0.03-0.24)(46)	Test developed for use by specialist psychiatrist Time-consuming test (>5 mins) Useful for research reference diagnostic testing Allows for severity rating
6. MDAS	10-item, 4-point clinician-rated scale designed to quantify the severity of delirium. Scale reflects the DSM-IV criteria for delirium	E	Yes	MDAS ≥10: Overall sensitivity and specificity of 92% (95%CI: 75-98) and 92% (95%CI: 70-98) summary positive and negative likelihood ratios of 12 (95%CI: 2.4-58) and 0.09 (95%CI: 0.02-0.38) (46)	Allows for assessment of delirium severity and repeated measures. Time-consuming (>10 mins)

*Suitable for non-expert clinicians and adapted versions for nursing staff with training. However, lower sensitivities found e.g. in the ICU with nurses performing the CAM (14).

[§]Overall performance figures are from predominantly elderly medical in-patient or post-operative surgical cohorts only (46). Performance outcomes for different patient populations and other clinical settings such as nursing homes and ICU are not shown.

ODSM: Operationalised Diagnostic and Statistical Manual, 4th edition; CAM: Confusion assessment method; MMSE: Mini-mental state examination; DRS: Delirium rating scale; DRS-Revised 98: Delirium rating scale-revised-98; MDAS: Memorial delirium assessment scale

B. Screening

Bedside delirium instrument	Description	Expert or non-expert tester	Training needed	Overall performance[§]	Comments/suitability to developing country settings
1. DOSS	Original version consisted of 25-item scale based on DSM-IV criteria. Design to detect early symptoms of delirium that nurses could observe during regular care. Subsequently scale was reduced to 13-observation	NE	Yes	Overall sensitivity and specificity of 92% (95%CI: 74-98) and 82% (95%CI: 66-92) and summary positive and negative likelihood ratios of 5.2 (95%CI: 2.7-9.9) and 0.10 (95%CI: 0.03-0.37) (46)	Useful tool able to be completed in less than 5 minutes by trained nurses Sub-optimal specificity limits use as reference for research studies, but good sensitivity offers clinical utility as a screening test Not cognitive test Unaffected by education level and English language proficiency
2. GAR	Physician-rated 10-cm visual analog scale in which a high rating indicates the patient can be easily engaged and a low rating indicates the patient cannot be aroused. Assessment is based on a minimum of 2 minutes of general conversation (46)	E	No	GAR<7: **Single prospective study** showed sensitivity and specificity of 94% (95%CI: 73-100) and 99% (95%CI: 92-100) and positive and negative likelihood ratios of 65 (95%CI: 9.3-458) and 0.06 (95%CI: 0.01-0.38) (46, 60)	Able to be completed during 2 minutes of routine patient interview. Specific test training not required but screening tool developed for and only used by geriatricians with clinical experience during MMSE testing Unaffected by education level and English language proficiency
3. Nu-DESC	Screening scale designed to be administered by a nurse based on clinical observation in routine practice	NE	Yes	Nu-DESC>0: **Single prospective study** showed sensitivity and specificity of 96% (95%CI: 80-100) and 69% (95%CI: 59-79) and positive and negative likelihood ratios of 3.1 (95%CI: 2.3-4.4) and 0.06 (95%CI: 0.01-0.40) (46, 61)	Able to be completed by nurse in 1 minute Nurses require training to allow symptom rating Sub-optimal specificity
4. AMT	10-item short cognitive screening tool. Domains assessed include orientation, attention, immediate recall and long-term memory	NE	No	AMT <8: **Single prospective study** showed sensitivity and specificity of 92% and 65% with a positive likelihood ratio of 2.6 (62) Other studies showed good correlation with other in-depth cognitive assessment tools but no specific sensitivity and specificity figures (63, 64)	Suitable for non-experts with minimal training Shortened versions (AMT7, AMT5 and AMT4) are shortest available cognitive screening tools in clinical practice (65, 66) Cognitive screening tool therefore unable to differentiate dementia from delirium Uncertain impact of education and language barriers, likely less than MMSE (54)
5. Digit span test	At a rate of 1 per second a series of random numbers are presented. Starting with a 2-number sequence, patients must correctly repeat each series. The next sequence has 1 additional digits and the test is abnormal if the patient cannot repeat at least 5 digits (46)	NE	No	Sensitivity and specificity of 34% (95%CI: 22-48) and 90% (95%CI: 97-93) in one study and subsequently, in a recent study, 77% and 78% respectively (46, 67, 68)	Minimal training and <1minute to preform No problem with literacy and language Not useful as a rapid rule-in test as very low sensitivity
6. Vigilant "A" test	Patients are read a list of 60 letters containing the letter "A" 18 times. Letters are read at a rate of 1 per second and the patient is asked to indicate when the letter "A" is spoken (46)	NE	No	**Single prospective study** showed sensitivity and specificity of 61% (95%CI: 47-74) and 77% (95%CI: 73-81) and positive and negative likelihood ratios of 2.7 (95%CI: 2.0-3.5) and 0.50 (95%CI: 0.36-0.71) (46, 67)	Minimal training and only 1minute to preform No problem with literacy and language Sub-optimal sensitivity and specificity limits rule-in or rule-out clinical utility

[§]Overall performance figures are from elderly medical in-patient cohorts only. Performance outcomes for different patient populations and other clinical settings such as nursing homes, ICU and surgical units are not shown.

DOSS: Delirium observation screening scale; GAR: global attentiveness rating; Nu-DESC: Nursing delirium screening scale; AMT: Abbreviated mental test

Delirium diagnostic instruments

The most widely used bedside diagnostic instrument with the best available supporting data is the confusion assessment method (CAM) (55). The CAM was developed by Inouye and colleagues in 1990 based on an extensive literature review, geropsychiatric consensus and the DSM-IIIR criteria (69). It was designed to allow non-psychiatric clinicians to diagnose delirium quickly and accurately following brief formal cognitive testing (55). The CAM has now been adapted for use in the ICU, emergency department and chronic care setting and translated into ten languages (55). Two recent meta-analyses found that, in general medical in-patient settings, the CAM had an overall sensitivity and specificity of 94% (95% Confidence interval, CI 91-97%) and 89% (95% CI 85-94%) and summary positive and negative likelihood ratios of 9.6 (95% CI 5.8-16.0) and 0.16 (95% CI 0.09-0.29) respectively (46, 55). The CAM test is proposed as a rapid (<5 minute) diagnostic tool that can be performed by non-experts (46). However, Wei et al., in their recent meta-analysis, highlight that the CAM was designed to be scored based on observations made during formal cognitive assessment (55). Both a failure to perform cognitive testing and inadequate CAM training for non-expert testers has been shown to compromise test sensitivity (55). Thus, although the CAM has the potential for use as a sensitive, rapid delirium screening tool, these limitations are likely to restrict its use in routine clinical settings to trained non-expert clinicians or highly trained nurses e.g. ICU sisters. In addition, these limitations also reduce its suitability and potential routine use in over-stretched resource-limited healthcare settings such as found in the majority of developing country hospitals.

Although little, if any, formal cognitive testing is performed in routine hospital care in the majority of developing country settings, the MMSE, a 30-item brief cognitive testing tool, is the most familiar and utilised of available validated cognitive and delirium testing tools. The MMSE was originally designed as a brief (5-10 minute) practical clinical instrument for distinguishing functional from organic mental-status impairment (50). It has been most studied as a tool for dementia screening in elderly patient cohorts, but has also been widely used and studied for both the diagnosis and screening of delirium (50, 57, 70). However, its use as a delirium instrument, particularly in developing country settings, has a number of limitations. Firstly, being only a cognitive testing tool it is unable to differentiate delirium from other forms of organic cognitive impairment e.g. dementia. Consequently, the MMSE, using an accepted cut-point of less the 24, when compared to the other delirium diagnostic instruments shown in table 3A, has poor specificity and a low positive likelihood ratio [1.6 (95%CI: 1.2-2.0)] (46). Secondly, MMSE performance has been found to been negatively influenced by poor educational levels and language proficiency (50, 52, 53, 58, 71). The normalization of test scores for age and educational level (59) has to some extent mitigated these drawbacks but the test is not recommended for non-fluent English speakers or patients without at least a primary school education (50, 71). Nevertheless, the fact that the items of the MMSE have been very well standardized for use by non-expert lay testers, has meant that even in developing countries with predominantly non-native English speakers and poor educational and literacy levels, it is widely available for brief formal cognitive testing and delirium screening in hospitals. Unfortunately,

though, despite its availability and advocacy as a delirium screening and brief cognitive testing tool, its uptake and daily use by healthcare workers in time-constrained routine clinical practices is limited by the time required (5-10 minutes) for test completion as well as by other aforementioned difficulties.

Delirium screening instruments and use in developing countries

In developing country hospital settings, the use of rapid (<2 minutes), easy-to-perform, education and language-independent delirium screening tools that can be performed by non-expert testers after minimal training are likely to have the greatest uptake and utility in routine hospital practice. A number of evaluated rapid delirium screening tools and their performance in predominantly older medical in-patient cohort studies are shown in table 3B. Single domain (attention) non-cognitive tests e.g. the global attentiveness rating (GAR) or the vigilance 'A' test are appealing as they take two minutes or less to perform, however, sensitivity is less than 50% unless performed by expert clinicians (60). Other potentially applicable screening tools for non-experts such as the Nurse delirium screening scale (Nu-DESC) have shown good sensitivity, are education and language independent, and able to be performed in less than five minutes (7, 46, 61, 72). The need for initial training and ongoing review potential limit their widespread use. The abbreviated mental test (AMT), a validated cognitive test able to be performed by non-experts with no training in less than two minutes, appears to potentially suited to younger medical cohorts in developing countries.

Abbreviated mental test (AMT)

The 10-item AMT was developed in 1972 by Hodkinson (63) from the modified Roth Hopkins Test (73, 74). It was originally evaluated for use as a brief screening tool for cognitive impairment in elderly hospital patients and found to correlate well, and be more acceptable to clinician's, than the longer, original Roth Hopkins test (75). The correlation of the AMT with other cognitive testing tools and its' inter and intra-observer reliability has been assessed in a range of elderly patient settings including long-stay care (75), residential home (76), and psychogeriatric outpatients (77). It has been evaluated for dementia screening amongst elderly patient cohorts from a number of different developed countries (78-80). In addition, modified shortened 7, 5, and 4-question versions of the AMT, developed using elderly patient populations have shown good correlation with the full 10-question AMT and the other cognitive tools such as the MMSE (65, 66). Few studies have evaluated the AMT using final diagnosis or patient outcomes (66), and the test has not been extensively studied as a rapid screening tool for delirium. In a cohort of 184 new hospital admissions to the geriatric unit at the Royal London Hospital, Jitapunkul et al. found the AMT to have a sensitivity of 92% for the diagnosis of delirium (62). Similar to the MMSE, the AMT is not able to differentiate delirium from dementia, and hence specificity in older cohorts with high dementia prevalence is sub-optimal and diagnostic tools with greater specificity would be preferred. The AMT has not been evaluated in younger general medical cohorts from developing country settings. The ease-of-performance by non-experts, lack of training requirements, and speed of performance (<2 minutes) together with relative un-importance of

differentiating delirium from dementia in younger patient cohorts, makes its' use for delirium screening in younger medical in-patients particularly appealing. The only drawback may be the potential impact of educational level and language proficiency on test performance in this setting, however this is likely to be less of a factor than with the MMSE (54). The evaluation of the AMT, and the potential development of modified shorter versions of this test for use in younger medical in-patients are now urgently required.

Study aims

In this context, the objectives of the study were threefold. Firstly, to determine the prevalence, risk factors and outcomes of delirium in a young medical in-patient cohort from a high HIV-prevalent developing country setting. Secondly, to evaluate the performance of the abbreviated mental test (AMT) as a rapid delirium screening tool when performed by junior medical doctors at the time of medical admission. Thirdly, using logistic regression modeling techniques, to develop a shortened version of the AMT. This shortened AMT would be able to be performed in less than 1 minute, easily committed to memory by non-expert healthcare workers e.g. junior doctors, and be independent of patient's level of education or the use of a translator, thereby being ideally suited to widespread uptake and routine clinical use.

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Title:

The 4-"RACY"-questions for rapid delirium screening in general medical in-patients

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Abstract

Objectives: To develop a concise rapid delirium screening instrument to identify general medical in-patients with delirium.

Design: Prospective observational cohort study.

Setting: General medical wards of Groote Schuur Hospital, Cape Town, South Africa.

Participants: 459 medical in-patients older than 16 years.

Outcome measures: Routine delirium testing and barriers to testing. Delirium prevalence and outcomes. Diagnostic accuracy of abbreviated mental test (AMT) and newly developed 4-question "RACY" delirium screening tool.

Results: The median (IQR) age was 45 (31-60) years. Delirium was diagnosed in 20.3% (95%CI: 16.4-24.2) of patients. Delirium was associated with an increased in-patient mortality [OR 3.9 (95%CI: 1.6-9.3), p=0.002] and >7 days hospitalisation [OR: 2.4 (95%CI: 1.2-4.7), p=0.01]. No patient diagnosed with delirium received any formal cognitive testing at the bedside as part of routine care. The newly developed 4-question "RACY' screening tool demonstrated equivalent diagnostic performance to the 10-question AMT, irrespective of the patient's education level, or use of a translator. Using the optimal ROC-selected cut-point of RACY≤2, the sensitivity, specificity, and positive and negative predictive values were 78% (95%CI: 67-86); 85% (95%CI: 80-89); 56% (95%CI: 46-65); and 94% (95%CI: 91-96) respectively.

Conclusions: Although the prevalence of delirium was 20% amongst non-geriatric medical in-patients and associated with poor clinical outcomes, no bedside delirium screening tools were used in routine clinical care. The novel 4-question “RACY” screening tool has the potential to be a simple but effective bedside delirium diagnostic instrument for use in non-geriatric general medical in-patient settings. Its performance was not affected by patient education level and/or the use of a translator.

Word count: 257/300

Article summary

What is already known on this topic

Delirium is common amongst predominantly elderly, general medical in-patients and is associated with poor short-, medium-, and long-term outcomes

A number of standardised bedside instruments are available for delirium testing in different settings, but routine clinical use and suitability to busy general medical wards is variable.

What this study adds

Despite admission to a tertiary academic hospital, no patients in this cohort received any cognitive testing or formal delirium screening during the initial 48 hours following admission

Delirium was prevalent in 20% of non-geriatric general medical in-patients and was associated with poor outcomes. Routine bedside screening for delirium should be a mandatory component of clinical care for all general medical in-patients, not just geriatric patients

The novel 4-question "RACY" screening tool offers potential as a rapid (<2 minute), simple and effective bedside delirium diagnostic instrument for use in non-geriatric general medical in-patients, independent of patients' education level and use of a translator

INTRODUCTION

Delirium is a serious medical condition associated with increased mortality, longer hospital stay, increased rates of institutionalisation, and declines in post-admission functionality (1-4). Studies in geriatric, intensive care, and post-operative surgical cohorts have identified a number of risk factors for delirium, and shown the benefit of multidisciplinary interventions to prevent and manage this condition. (1, 5-11). However, despite the simplicity and low cost of many of these interventions, little information on delirium in younger cohorts of general medical in-patients is available.

There is also a paucity of data on delirium from developing countries settings such as South Africa, where the characteristics of general medical in-patients are unique. The median age of in-patients is lower, there is a dual burden of communicable and non-communicable diseases, and in-patient and 12-month mortality rates are equivalent to those of intensive care units (ICUs) and geriatric cohorts in developed countries (12, 13). These factors, together with the known association of delirium with adverse outcomes, suggest that routine delirium diagnosis would be clinically useful, and should be mandatory. In practice, however, the under-diagnosis of delirium by healthcare workers in general medical in-patient settings remains an ongoing problem (14).

A routine clinical assessment is insensitive for the identification of a delirious patient; instead, the diagnosis relies on the use of validated bedside instruments (1). Standardised tools such as the confusion assessment method (CAM) have been developed and validated in a wide variety of settings (14, 15). Their use has simplified and improved the detection of delirium in many hospital and intensive

care settings (15, 16). However, in many countries, their use remains limited to geriatric units and ICUs (14) because they still require practitioner training, sufficient time for administration, and adequate patient educational and language levels (14, 17). In overburdened care environments typical of the general medical admission wards of most developing countries, these requirements are seldom completely met. A need exists for the development and validation of effective, education- and language-independent delirium screening tools that can be performed rapidly (in less than 2 minutes) by untrained non-expert clinicians.

The objective of this study was to develop an easily administered, effective screening tool to be utilised by non-expert testers to recognise delirium amongst general medical in-patients.

METHODS

Study population

Our study population consisted of a cohort of 459 patients admitted to the acute general medical wards at Groote Schuur Hospital (GSH), Cape Town, South Africa, between 14 September 2009 and 16 November 2009. Any patient older than 16 years of age referred from either the emergency unit or a district-level hospital for admission to the general medical wards was eligible for inclusion. Patients directly admitted to palliative care beds (where death is anticipated within 48 hours of admission), and those admitted to the "short-stay ward" (where patients with predominantly chronic disease and an anticipated hospital stay of less than 48 hours are admitted) were not eligible for enrollment. Verbal consent was taken from all patients and the study received ethical approval from the University of Cape Town Human Research Ethics Committee. On admission, all baseline demographic information (including highest level of education), clinical and laboratory data, and pre-admission functionality data were collected. The modified early warning score (MEWS) was determined by basic clinical parameters at the time of admission and was used as a score of illness severity (18). After discharge, folders underwent blinded review to document primary diagnosis necessitating admission, and up to two relevant underlying chronic medical conditions. All enrolled patients had attempted follow-up at 12-months with telephonic or home interviews to ascertain mortality status and assess functionality. All folders were reviewed for any documentation of delirium or evidence of routine formal bedside cognitive testing within 48 hours by the admitting clinicians.

Delirium testing within the study

Two independent testers screened all patients meeting the eligibility criteria described above for delirium within 48 hours of admission. Patients were excluded from delirium testing if they were admitted directly to the intensive care unit (ICU), had a Glascow coma scale (GCS) rating <12, died prior to testing, were aphasic, or refused consent. A specialist physician (expert tester) performed an in-depth patient interview of at least 30 minutes duration that included scoring of the confusion assessment method (CAM) (19) and, where possible, the mini-mental state examination (MMSE). The expert testers (4 in total) were qualified specialists trained in the DSM-IV criteria and CAM assessment method. The MMSE was only performed if patients were able to read and write and had more than six years of formal education (17, 20). Prior to the start of the study, all study physicians received training on the use of the confusion assessment method and the DSM-IV criteria for delirium diagnosis. Delirium was diagnosed if both the CAM and MMSE were abnormal (MMSE≤24) (17). When the two tests disagreed, the overall expert tester's assessment during the in-depth interview was used for final delirium classification. Thus, the combination of CAM, MMSE and physician's overall assessment during in-depth interview formed a composite reference standard. Independently, a junior doctor (non-expert), blinded to the other test results, performed a locally adapted Hodgkinson's abbreviated mental test (AMT) (21) within 48 hours of reference testing (see online supplementary methods). The presence of a language or any other barrier to the use of the CAM, MMSE and AMT delirium screening tools was documented.

Statistical analysis

Simple descriptive statistics were employed to describe the study population, and the patients with/without delirium were compared using χ^2, Fisher's exact and Kruskal-Wallis tests where appropriate. Logistic regression analysis was used to calculate odds ratios and 95% confidence intervals for outcome measures associated with delirium. The regression model was adjusted for age, sex, race, HIV-infection, non-independent pre-admission activities of daily living (ADLs), the presence of a language barrier and ≤ of formal education, illness severity (MEWS) and a primary admission diagnosis of TB. Logistic regression analysis was used to develop the shortened 4-question "RACY" tool. More detailed methods are outlined in the online supplement. Overall performance of both the 10-question AMT and 4-question "RACY" was evaluated using the area under the receiver operating characteristic (AUROC) curve. ROC curves for 10-question AMT and 4-question "RACY" performance in different educational strata were compared. 10-question AMT and 4-question "RACY" sensitivity, specificity, and positive and negative predictive values with 95% confidence intervals for different ROC-selected cut-points were calculated. STATA IC version 10 (Stata Corp, Texas, USA) was used for all statistical analyses. Study reporting and analysis were consistent with the STARD criteria (22).

RESULTS

Study population

Figure 1 outlines the study patient flow. In total, 465 patients referred for admission to the acute general medical wards during the nine-week study period were considered for enrollment. Six patients with age ≤16 years were excluded, and 459 patients were enrolled. 11.1% (51/459) of patients were excluded from delirium testing (19 patients with GCS <12, 15 aphasic patients, 6 patients with direct ICU admission, 4 patients refusing consent, 3 patients deceased prior to testing). Overall, the 12-month cohort mortality was 42.3% (95% CI: 37.7-46.8, 194/459), with in-patient and 12-month mortality being 10.9% (95% CI: 8.0-13.7, 50/459) and 35.2% (95% CI: 30.6-39.8, 144/409) respectively. The median (IQR) length of hospital stay was 6 (4-11) days and 17.8% [(95% CI: 13.8-21.7, 64/360) (49/409 missing discharge information)] of patients were discharged to a convalescent care facility.

Notably, in no cases did any patient receive routine formal cognitive testing independent of the study itself.

Study-related delirium screening and barriers to testing

Figure 1 highlights patients undergoing study-related delirium screening with the CAM, MMSE, physician assessment, and AMT. Only 1 patient did not receive a CAM and physician assessment. 51% (207/409) of patients were unable to complete a full MMSE. 4.4% (18/409) of patients did not have any AMT result, while a further 2.2% (9/408) only received an AMT more than 48 hours after

reference testing. 53.2% (217/408) of patients were documented as having a barrier to delirium testing with one/all of the CAM, MMSE, and AMT. Barriers included: i) 25.4% (104/408) of patients had a educational level ≤ 7 years (major barrier to full MMSE completion; ii) 17.6% (72/408) of patients required the use of a translator to complete the interview; iii) 2.7% (11/408) had visual impairment; iv) 2.9% (12/408) had physical writing difficulties; and v) 4.4% (18/408) had other difficulties including hearing impairment, dysarthria, and medical instability. Only two and four patients undergoing delirium testing were known with dementia and depression respectively. In all patients with barriers to testing, in-depth interviews and diagnostic classification were still able to be completed. Delirium occurred more frequently in patients with <7 years of education and this increased the likelihood of delirium [OR: 2.1 (95% CI: 1.1-4.0), p=0.03]. No differences in delirium prevalence were noted between patients with and without other testing barriers.

Delirium prevalence and screening tool agreement

Using the composite reference standard, the prevalence of delirium was 20.3% (95% CI: 16.4-24.2, 83/408). Using CAM alone, the prevalence of delirium was 17.4% (95% CI: 14.0-20.9, 80/408). In 62.7% (52/83) of patients diagnosed with delirium using the composite reference standard, it was impossible to complete an MMSE. In patients where MMSE was performed, CAM and MMSE agreed in only 75.6% (189/250) of cases. The physician's assessment, made after the administration of at least one of the standardised tools and using the DSM-IV criteria, was required for final diagnostic classification in 53.6% (219/408) of cases where the MMSE was absent or discordant with the CAM.

Demographics, admission diagnoses, and delirium

Table 1 shows basic patient characteristics stratified by delirium diagnosis. Overall, study patients had a median (IQR) age of 45 (31-60) years, with no age difference between patients with and without delirium. 57% (260/459) and 21% (96/459) of patients had > 7 years of formal education or an unknown education level, respectively. An education level of >7 years occurred more frequently in patients without delirium [69% (225/325) vs. 39% (32/83), p<0.001], while an unknown educational level was more common amongst patients with delirium [33% (27/83) vs. 7% (22/325), p<0.001]. Delirium occurred less frequently in patients that were independently performing activities of daily living (ADLs) prior to hospitalisation [19% (62/325) vs. 47% (39/83), p<0.001]. Considering illness severity, the overall median (IQR) MEWS was 2 (1-4). MEWS was higher in patients with delirium vs. no delirium [3 (2-5) vs. 2 (1-3), p<0.001].

Table 2 outlines the most common admission and underlying chronic diagnoses stratified by delirium diagnosis. Non-TB community acquired pneumonia, TB, cerebrovascular accident (CVA), congestive cardiac failure, and primary central nervous system (CNS) infections accounted for 54% (246/459) of all primary admission diagnoses. All other primary admission diagnoses occurred with prevalence of 5% or less and were not associated with any of the main outcome measures. TB (pulmonary and extra-pulmonary forms combined) and acute renal failure (ARF) occurred more commonly in patients diagnosed with delirium [TB: 23% (19/83) vs. 13% (43/325), p=0.03; ARF: 11% (9/83) vs. 5% (15/325), p=0,03]. HIV-infection was the most common underlying chronic illness with a prevalence of 32% (145/459). HIV-infection was not significantly

higher amongst patients diagnosed with delirium (p=0.2). 15% (69/459) and 12% (57/459) of patients had underlying hypertension and diabetes respectively, and these two conditions were the commonest underlying non-communicable chronic illnesses.

Delirium outcomes and risk factors

Table 3 shows the important short- and medium-term patient and health system outcomes associated with in-patient delirium. Using the composite reference, in-patient delirium increased the likelihood of in-patient mortality [OR: 3.9 (95% CI: 1.6-9.3), p<0.001], 12-month mortality [OR: 3.4 (95% CI: 1.4-7.9), p=0.005], discharge to convalescent care facility [OR: 5.5 (95% CI: 2.8-10.9), p<0.001] and length of hospital stay >7 days [OR: 2.4 (95% CI: 1.2-4.7), p=0.01]. Age, non-independent pre-admission ADLs, and the presence of delirium were the only variables associated with in-patient mortality.

Diagnostic accuracy of 10-question abbreviated mental test (AMT10) for delirium screening

93.4% (381/408) of patients undergoing composite reference delirium screening had a matching AMT performed within 48 hours of the reference testing. Figure 2A shows a ROC-curve of the overall diagnostic accuracy of the AMT10 for in-patient delirium and a corresponding table of performance characteristics at different test cut-points. The AUROC for the AMT10 is 0.89. The AUROC did not change significantly if test results were stratified by: i) formal education ≤ 7 years vs. > 7 years (AUROC: 0.80 vs. 0.86, p=0.4) and ii) tester-patient language discrepancy present vs. absent (AUROC: 0.87 vs. 0.89, p=0.8). At

the previously validated cut-point of AMT<8, the sensitivity, specificity, and positive and negative predictive values (PPV, NPV) were 77% (95% CI: 66-85), 85% (95% CI: 81-89), 55% (95% CI: 46-65), and 94% (95% CI: 90-96) respectively. Using a ROC-selected cut-point of AMT≤6, compared to the suggested cut-point of AMT<8 improved test specificity [92% (95% CI: 89-95) vs. 85% (95%CI: 81-89), p=0.006], without a significant loss in sensitivity [68% (95% CI: 56-77) vs. 77% (95% CI: 66-85), p=0.2]. Using an AMT≤6 could correctly rule-out delirium in 74.0% (282/381) of patients, with less than 1 in 20 patients inappropriately diagnosed with delirium. Using the cut-points of AMT<10 and ≤4 to optimise rule-out or rule-in test utility significantly compromised test specificity or sensitivity respectively.

Development and diagnostic accuracy of the 4-question "RACY" delirium screening tool

Using logistic regression modeling, 4/10 questions of the AMT were found to have the same predictive abilities as the full AMT for the diagnosis of delirium. These 4 questions were: i) "R": Recognising the roles of 2 people (e.g. doctor and nurse); ii) "A": recalling a short Address; iii) "C": Counting backwards from 20 to 1; and iv) "Y": naming the current Year. The use of the acronym "RACY" provides a useful memory aid for clinicians. Detailed tables and figures comparing models with different question combinations and previously validated shortened AMT test versions (23, 24) are provided in the online supplement. Figure 2B shows a ROC-curve of the overall diagnostic accuracy of the "RACY" 4-questions for in-patient delirium and a corresponding table of performance characteristics at different test cut-points. The AUROC for the "RACY" 4-questions is 0.89. The AUROC did not differ significantly from the AUROC of the AMT10. The AUROC

did not change significantly if test results were stratified by: i) formal education <7 years vs. > 7 years (AUROC: 0.80 vs. 0.90, p=0.17); and ii) tester-patient language discrepancy present vs. absent (AUROC: 0.88 vs. 0.90, p=0.8). At the best overall cut-point of RACY≤2, the sensitivity, specificity, and positive and negative predictive values (PPV, NPV) were 78% (95% CI: 67-86); 85% (95% CI: 80-89); 56% (95% CI: 46-65); and 94% (95% CI: 91-96) respectively. Using a cut-point of ≤2, RACY could correctly rule-out delirium in 68% (241/353) of patients, with less than 1 in 20 patients inappropriately diagnosed with delirium. Using alternative cut-points of RACY≤3 and ≤1 to optimize rule-out or rule-in test utility significantly compromised test specificity or sensitivity respectively.

DISCUSSION

Delirium is a common, serious medical condition consistently associated with poor short- and long-term morbidity and mortality, and substantial healthcare costs (1, 2, 25). In the elderly, it is one of the commonest preventable adverse events related to hospital admission (27,28) and is an important indicator of health care quality in this patient group (1). Advancing age is considered the key patient vulnerability associated with the development of the delirium (1), and to date, the majority of research and clinical care initiatives for delirium have focused on the elderly. Little data from younger general medical in-patients populations are available, and few bedside delirium instruments tailored to these clinical settings have been developed and validated.

Our study shows that amongst a younger medical in-patient cohort with a mean age of only 45 years, delirium prevalence was 20% in new hospital admissions, and was associated with increased in-patient and 12-month mortality, longer hospital stay and increased convalescent care facility discharge. The prevalence of delirium of 20% and its associations with poor short- and medium-term outcomes are similar to figures from geriatric in-patient cohorts (2). This highlights the need for an increased awareness and recognition of delirium amongst non-geriatric medical in-patients, especially in settings with high dual burdens of communicable and non-communicable diseases.

Undirected bedside assessment for delirium is ineffective, with studies showing that healthcare workers consistently document delirium poorly, and identify less than fifty percent of cases in routine clinical practice (14). In response to this, a number of bedside delirium testing instruments have been developed, validated

and made available (14). Instruments such as the CAM have been widely adopted and are utilised in routine clinical care settings including geriatric units, medical in-patient wards, surgical post-operative wards and ICUs (15). Our study, however, highlights that the usage of tools such as the CAM, even in tertiary hospital settings, is sub-optimal. In this study, formal cognitive testing and delirium screening were not performed as part of routine clinical care for any new general medical admission during the initial 48 hours of their hospital stay. A number of factors may contribute to this neglect of delirium screening, including: i) the perceived complexity of available tools to diagnose delirium, and a lack of tester training; ii) the time required to perform cognitive testing in busy routine clinical settings; and iii) tester-patient language discrepancy and the lack of locally modified and validated screening tools. There remains a need for the development of delirium screening tools that are effective, validated, easy to learn by non-expert testers, and quick to administer.

In busy routine clinical environments it is likely that only simple, easily learnt diagnostic screening tools will be widely utilised. Study of the widespread use of short screening tools like the 4-question CAGE alcoholism instrument in primary care and developing country settings supports this notion (26, 27). In this study we have developed the novel, 4-question "RACY" delirium screening tool, based on the 10-question AMT. We demonstrate its potential to perform as a rapid, simple but effective delirium screening tool correctly diagnosing delirium in close to 80% of hospitalised general medical patients, independent of patient education level and use of a translator.

The AMT was originally developed from the modified Roth-Hopkins test by Hodkinson in 1972 (21), and has been widely validated and used as a brief

cognitive testing tool predominantly to screen for dementia in elderly patient cohorts (28-31) . For delirium testing, it showed a sensitivity of >90% in a hospitalised elderly cohort, but was unable to distinguish delirium from dementia (32). In addition, 7-, 5- and 4-question shortened versions of the AMT have been shown to offer equivalent performance to both the 10-question AMT and the MMSE for dementia screening in the elderly (23, 24). To date, despite the reduced need to distinguish dementia from delirium in younger medical in-patients, neither the 10-question nor the shortened versions of the AMT have been evaluated for delirium screening in general medical cohorts. Other rapid (< 1 minute), simple delirium screening tools developed for non-expert testers such as the vigilance 'A' and Digit span tests have been evaluated in developing country settings, but show sub-optimal sensitivity and inferior overall diagnostic accuracy when compared to the 4-question "RACY" screening tool (33, 34).

Our study had a number of important limitations. Firstly, although the study included a large number of medical in-patients, only a single hospital was used for patient recruitment, potentially limiting generalisability of study findings to other settings. However, South African tertiary hospitals, with dual burdens of communicable and non-communicable diseases offer a more generalisable medical in-patient sample than many other single tertiary hospital settings (13). Secondly, the presence of testing barriers and inability to perform an MMSE in over 50% of patients created a need to rely on expert assessment for reference delirium diagnosis. This limitation is common in diagnostic studies of delirium given that delirium diagnosis is reliant on clinical bedside testing, and is mitigated by the fact that expert testing with training has been shown to perform as a reliable and reproducible method (17). Thirdly, the AMT was performed up

to 48 hours from the expert assessment and this may have impacted test results given the fluctuating nature of delirium.

Delirium diagnosis and management, despite a high prevalence and poor short- and medium-term outcomes amongst non-geriatric medical in-patient cohorts, remains neglected. A lack of healthcare worker awareness, barriers to the use of traditional standardised delirium screening tools, overstretched healthcare resources and the lack of rapid, simple and effective bedside screening tools contribute to this neglect. In this study, we highlight the extent of neglect and impact of delirium in younger general medical in-patients. We propose the novel "RACY" screening tool as a simple, user-friendly delirium screening tool, which functions well independent of patient education level and use of a translator. We expect that further studies to validate this tool in other settings will re-enforce its utility as a rapid and effective screening tool.

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Figure 1.

Study flow chart indicate patients tested with bedside delirium instruments

Figure 2.

Receiver operating characteristics curve and diagnostic accuracy measures for delirium at different AMT cut-points at a delirium prevalence of 18% for:

A. 10-question AMT (AMT10), and
B. 4-question AMT (AMT4)

Table 1. Patient characteristics for all study patients stratified by the delirium.

Patient characteristic	All (N=459) n (%)	Delirium (N=83) n (%)	No delirium (N=325) n (%)	P-values
Demographics, baseline education and functioning				
Age (median yrs, IQR)	45 (31-60)	46 (34-64)	43 (31-58)	n/s
Female	250 (55)	46 (55)	176 (54)	n/s
Race				
African	212 (46)	47 (57)	144 (44)	0.04
Mixed	202 (44)	31 (37)	147 (45)	n/s
Caucasian	36 (8)	4 (5)	27 (8)	n/s
Education level				
0-5 years	59 (13)	13 (16)	46 (14)	n/s
5-7 years	45 (10)	11 (13)	33 (10)	n/s
>7 years	259 (57)	32 (39)	224 (69)	<0.001
Unknown	96 (21)	27 (33)	22 (7)	<0.001
Non-independent pre-admission ADLs	113 (26)	39 (49)	62 (20)	<0.001
MEWS[#] (median, IQR)	2 (1-4)	3 (2-5)	2 (1-3)	<0.001

[#]MEWS: Modified early warning score. Scoring system using systolic blood pressure, heart rate, respiratory rate, temperature and the AVPU score to identify patients at risk for clinical deterioration, ICU admission and death (MEWS ≥5) (18).

Table 2. Primary admission and chronic underlying diagnoses for all study patients stratified by delirium.

Diagnosis	All (N=459) n (%)	Delirium (N=83) n (%)	No delirium (N=325) n (%)	P-values
Primary diagnosis necessitating hospitalisation				
NCD_CVD	92 (20)	15 (18)	56 (17)	n/s
CVA	46 (10)	8 (10)	19 (6)	n/s
Cardiac failure	37 (8)	6 (7)	29 (9)	n/s
Non-TB pneumonia	63 (14)	9 (11)	47 (15)	n/s
TB*	66 (14)	19 (23)	43 (13)	0.03
Primary CNS infection§	34 (7)	9 (11)	22 (7)	n/s
Acute renal failure	24 (5)	9 (11)	15 (5)	0.03
Cancer	17 (4)	3 (4)	13 (4)	n/s
Common underlying chronic medical illness				
HIV-infection	145 (32)	33 (40)	103 (32)	n/s
NCD_CVD	114 (25)	17 (21)	80 (25)	n/s
Hypertension	69 (15)	12 (15)	45 (14)	n/s
Diabetes	57 (12)	6 (7)	43 (13)	n/s
Valvular heart disease	19 (4)	0 (0)	17 (5)	0.05
COPD	21 (5)	3 (4)	18 (6)	n/s

*TB (tuberculosis): includes all patients with pulmonary TB, TB meninigits, disseminated TB and other extra-pulmonary forms of TB.
§Primary central nervous system (CNS) infections included all forms of meningitis (viral, bacterial and tuberculous), brain abscesses, encephalitis and opportunistic space-occupying lesions e.g. toxoplasmosis.
NCD_CVD= Non-communicable disease_Cardiovascular; CVA= Cerebrovascular accident; COPD = Chronic obstructive pulmonary disease

Table 3. Important short- and medium-term patient and health system outcomes associated with in-patient delirium (N=83).

Outcome	Odds Ratio (95% CI)	P-value
In-patient mortality	3.9 (1.6-9.3)	0.002
12-month mortality	3.4 (1.4-7.9)	0.005
Discharge to convalescent care facility	5.5 (2.8-10.9)	<0.001
Hospital length of stay > 7 days	2.4 (1.2-4.7)	0.01

Figure 1.

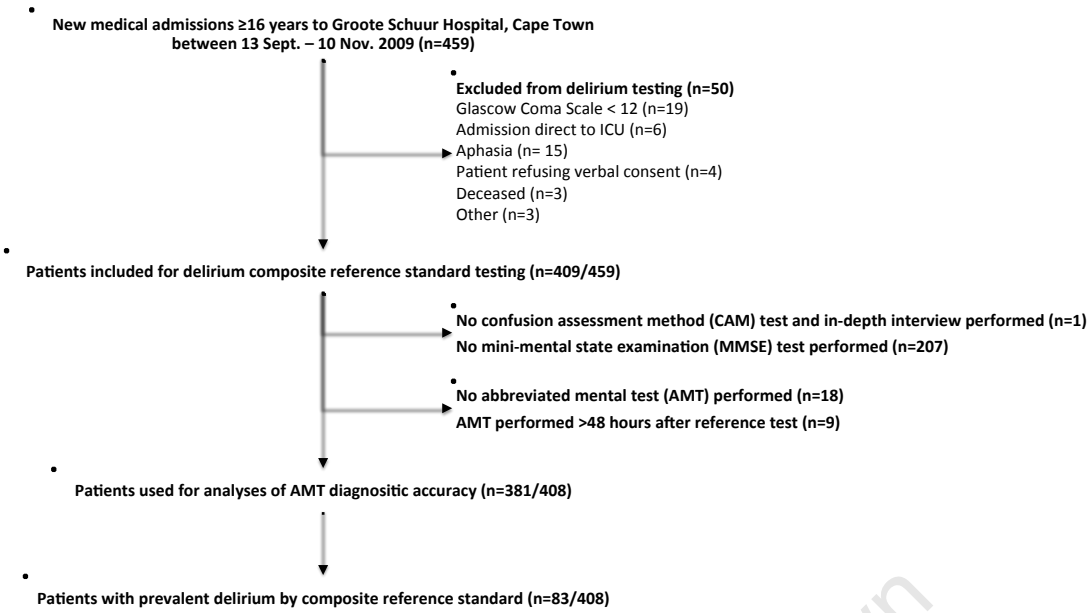
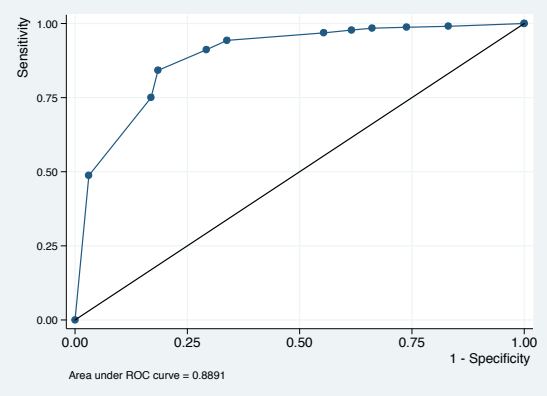
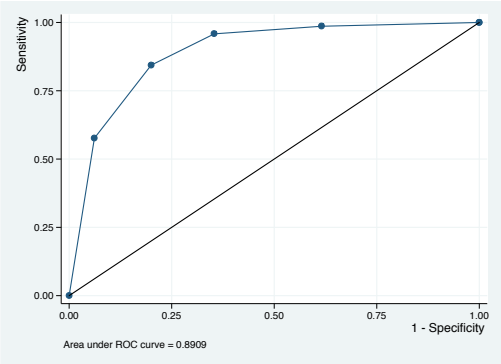


Figure 2.

A.



B.



Selection for type of test use (AMT10)				
	Rule-out	Standard	Overall (Youden's)	Rule-in
Cut-point	AMT <10	AMT <8	AMT ≤6	AMT ≤4
Performance characteristic (%, 95%CI)				
Sensitivity	96 (89-99)	77 (66-85)	68 (56-77)	41 (30-52)
Specificity	50 (45-56)	85 (81-89)	92 (89-95)	97 (95-99)
Positive predictive value (PPV)	32 (26-38)	55 (46-65)	68 (56-77)	77 (62-87)
Negative predictive value (NPV)	98 (95-99)	94 (90-96)	92 (89-95)	87 (83-90)

Selection for type of test use (RACY)			
	Rule-out	Overall (Youden's)	Rule-in
Cut-point	RACY ≤3	RACY ≤2	RACY ≤1
Performance characteristic (%, 95%CI)			
Sensitivity	93 (84-97)	78 (67-86)	62 (51-73)
Specificity	58 (52-64)	85 (80-89)	96 (93-98)
Positive predictive value (PPV)	35 (28-42)	56 (46-65)	80 (67-88)
Negative predictive value (NPV)	97 (93-99)	94 (91-96)	91 (88-94)

Conflicts of interest statement

"All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work"

Funding

No funding was utilized in this study. JP is currently supported by a Carnegie Fellowship award, SAMA PhD bursary and MRC Specialist under 45 awards.

Online supplementary material

Title:

The 4-"RACY"-questions for rapid delirium screening in general medical in-patients

JG Peter[1] *physician*, GL Calligaro[1] *physician*, S Pandie[1] *physician*, A Stanley[1] *physician*, R Homan[1] *intern*, H Hutton[1] *intern*, L Bertels[1] *intern*, Z Kerbelker[1] *intern*, S Naidoo[1] *intern*, R Sher[1] *intern*, S Baboolal[1] *intern*, L De Villiers[1] *geriatrician* and J Seggie[1] *professor in internal medicine*.

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Key words: delirium, diagnostic screening, abbreviated mental test (AMT), RACY screening tool

Author contributions: JP and JS designed the study. JP analysed the data and was the study statistician. All authors generated the data and were involved in the manuscript preparation.

Methods

Figure S1. Locally modified 10-question abbreviated mental test (AMT)

Abbreviated Mental Test Score

1)	What is your age? (± 5 years)	/1
2)	What is the time? (Nearest hour, or a.m. / p.m.)	/1
3)	Address for recall at the end of test: 42 Strand street	/1
4)	What is the year?	/1
5)	What is the name of this place? (GSH)	/1
6)	Recognition of two persons (i.e. doctor, nurse)	/1
7)	Date of birth (month and year)	/1
8)	Date of Christmas	/1
9)	Name of current South African president	/1
10)	Count backwards from number 20 to number 1	/1
	TOTAL	/10

Statistical analysis and development of 4-question RACY tool

Multivariate logistic regression analysis was used to develop diagnostic models for delirium from the 10-question AMT. Firstly, the log likelihoods of individual AMT questions were compared to select the question with the strongest predict ability. Thereafter, 2-5 question models were compared using the likelihood ratio test and the Akaike Information criterion (AIC) to compare nested models and select the simplest model. Overall performance of both the 10-question AMT and 4-question RACY was evaluated using the area under the receiver operating characteristic (AUROC) curve. ROC curves for 10-question AMT and 4-question RACY performance in different educational strata are compared. 10-question AMT and 4-question RACY sensitivity, specificity, positive and negative predictive values with 95% confidence intervals for previously validated and different ROC-selected cut-points were calculated. STATA IC version 10 (Stata Corp, Texas, USA) was used for all statistical analyses. Study reporting and analysis were consistent with the STARD criteria (1).

Results

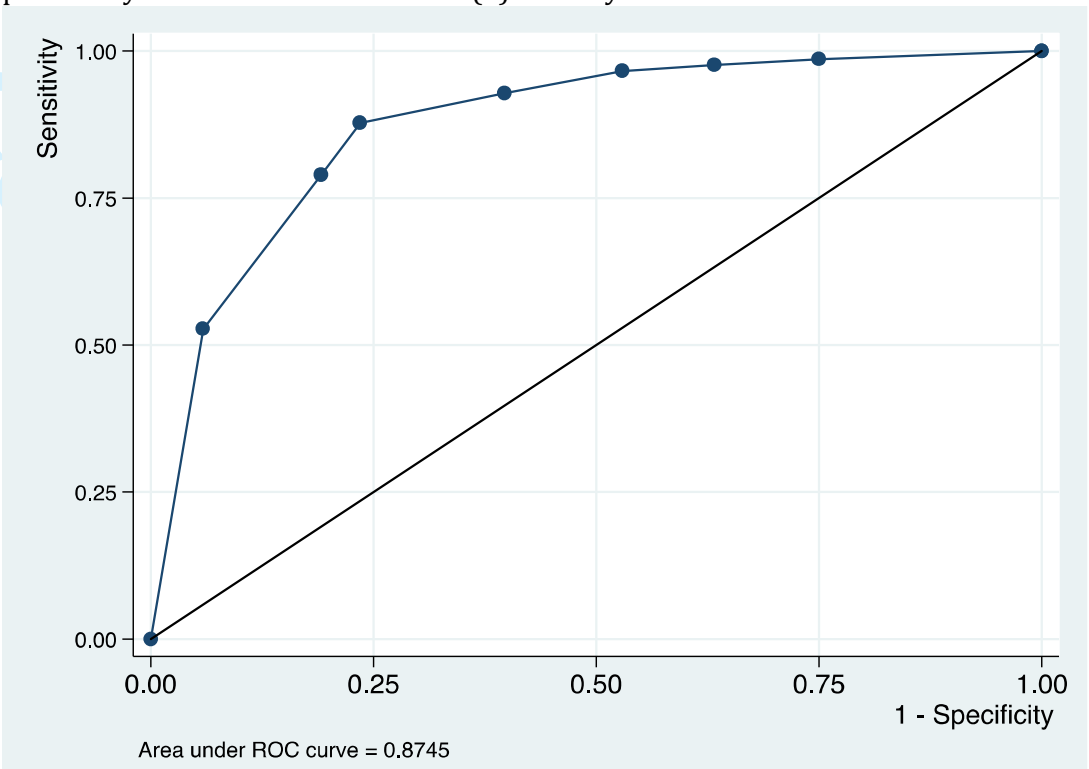
Table S1. Sensitivity and specificity of each AMT question for delirium diagnosis

Question no.	AMT item	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
1.	Age	23.3 (13.6-33.0)	96.9 (94.9-98.9)
2.	Time	54.8 (43.4-66.2)	91.0 (87.7-94.3)
3.	Address to recall	87.7 (80.1-95.2)	60.2 (54.6-65.9)
4.	Year	57.5 (46.2-68.8)	94.8 (92.3-97.4)
5.	Place (hospital name)	53.4 (42.0-64.9)	93.8 (91.0-96.6)
6.	Two person recognition	53.4 (42.0-64.9)	94.5 (91.8-97.1)
7.	Date of birth	39.7 (28.5-51.0)	94.5 (91.8-97.1)
8.	Important date recall	52.1 (40.6-63.5)	91.3 (88.1-94.5)
9.	Important person recall	52.1 (40.6-63.5)	88.6 (84.9-92.2)
10.	Count 20 backwards to 1	71.2 (60.8-81.6)	86.2 (82.2-90.1)

Table S2. Selected 1-5 question models illustrating selection of the simplest model of AMT questions with the best predictive ability for in-patient delirium

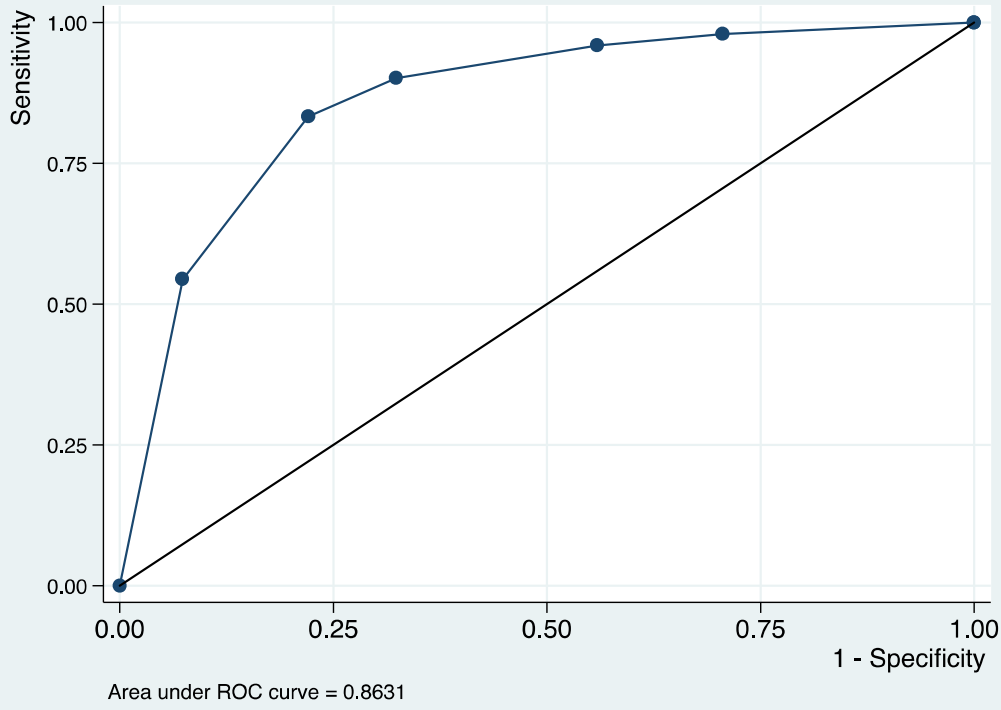
Model	Log like-lihood	Likelihood ratio test			AIC
		χ^2	P-value	Vs	
1. Question 4	-133.10	N/A	N/A	N/A	270.19
2. Question 4 & 10	-117.70	30.79	<0.001	1	241.40
3. Question 4 + 10 + 6	-113.12	9.16	0.003	2	234.25
4. Question 4 + 10 + 6 + 3	**-111.54**	**3.17**	**0.08**	**3**	**233.08**
5. Question 4 + 10 + 6 + 3 + 7	-111.54	0.00	0.96	4	235.07
6. Question 4 + 10 + 6 + 3 + 9	-111.43	0.22	0.64	4	234.85

Figure S2. ROC and performance characteristics at different cut-points for the previously defined shortened AMT7 (2) in study cohort



Selection for type of test use (AMT7)				
	Rule-out	Standard	Overall (Youden's)	Rule-in
Cut-point	AMT ≤6	AMT <5	AMT ≤3	AMT <2
Performance characteristic (%, 95%CI)				
Sensitivity	93 (85-97)	74 (63-83)	60 (49-71)	36 (26-47)
Specificity	53 (48-59)	88 (84-92)	94 (90-96)	98 (96-99)
Positive predictive value (PPV)	34 (27-40)	61 (51-71)	71 (59-81)	81 (65-91)
Negative predictive value (NPV)	97 (93-99)	93 (89-96)	90 (83-90)	86 (81-89)

Figure S3. ROC and performance characteristics at different cut-points for the previously defined shortened AMT5 (2) in study cohort



Selection for type of test use (AMT5)				
	Rule-in	Overall (Youden's)	Standard	Rule-out
Cut-point	AMT ≤1	AMT ≤2	AMT <3	AMT ≤4
Performance characteristic (%, 95%CI)				
Sensitivity	43 (32-54)	66 (54-76)	66 (54-76)	92 (83-96)
Specificity	96 (93-98)	91 (87-94)	91 (87-94)	55 (49-61)
Positive predictive value (PPV)	74 (59-84)	64 (53-74)	64 (53-74)	34 (28-41)
Negative predictive value (NPV)	87 (83-90)	91 (88-94)	91 (88-94)	96 (92-98)

References

1. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Ann Intern Med. 2003 Jan 7;138(1):W1-12.
2. Jitapunkul S, Pillay I, Ebrahim S. The abbreviated mental test: its use and validity. Age Ageing. 1991 Sep;20(5):332-6.

Part D: Supporting materials (Appendices)

D1. Covering letter to the BMJ editors

20 June 2012

Professor Fiona Godlee
Editor-in-chief
British Medical Journal

Dear Dr Godlee and colleagues,

Re: Peter *et al*. The 4-"RACY"-questions for rapid delirium screening in general medical in-patients

I would be most grateful if you would consider this manuscript for publication as an original article in the *BMJ*. The manuscript details delirium in a younger cohort of general medical patients and the development of the novel 4-question "RACY" delirium screening tool. The "RACY" screening tool offers potential as a concise and effective bedside delirium screening instrument for routine use in non-geriatric general medical in-patients.

Delirium is a common, serious medical condition known to be associated with poor outcomes. Yet, outside of geriatric and ICU settings, doctors in busy routine hospital practice rarely diagnose, document, or even consider delirium. Independent of our study team, not a single general medical patient amongst the 459 included in our study had any delirium screening or documentation during the first 48 hours following hospital admission, despite a delirium prevalence of 20% in this group. This oversight occurred despite the availability of a number of standardised bedside screening tools such as the well-validated confusion assessment method (CAM). Potential explanations for this include: i) the perception of delirium as a condition of the elderly; ii) the complexity of a number of standardised tools making bedside use, without prior training and/or memory aids, a challenge; iii) the lack of more than a few minutes to perform cognitive testing in busy routine hospital settings; and iii) uncertainty

regarding the performance of screening tools in environments where patient education is poor, tester-patient language discrepancy exists, and the use of translation may be required. Our study is in response to these challenges.

Our main study conclusions provide novel data highlighting the problem and impacts of delirium amongst younger general medical in-patients, while our newly developed "RACY" screening tool offers a potential solution to overcome the aforementioned barriers to delirium screening in routine clinical practice. Thus, the main findings of our study included:

i) Amongst a younger medical in-patient cohort, delirium occurred in 1 out of 5 new hospital admissions, and was associated with increased in-patient and 12-month mortality, longer hospital stay, and increased convalescent care facility discharge;

ii) Despite the availability of tertiary specialist services, no patients underwent routine cognitive testing or delirium screening during the initial 48 hours following admission to a general medical ward; and

iii) The "RACY" 4-question delirium screening tool offers a simple bedside delirium screening tool able to correctly diagnose delirium in close to 80% of hospitalised general medical patients, independent of patient education level or use of a translator.

These findings and the development of the simple "RACY" screening tool are novel. If uptake is similar to other successful 4-question screening tools e.g. the "CAGE" questions, we might hope that "RACY" may have a major impact on clinical practice. "RACY" has the potential to make delirium screening part of the admission assessment for all general medical patients; its potential ability to be used by non-specialist testers

in both developed and developing country general medical patients irrespective of tester-patient language discrepancy or patient education makes the tool widely applicable. Delirium is currently neglected despite the impacts on outcomes; yet, delirium is considered both preventable and amenable to therapy. Thus my co-authors and I believe that there might be an urgent need for a tool such as "RACY".

In terms of reviewers, might I suggest the following colleagues who have experience in the field of delirium and delirium diagnostic testing:

1. Camilla Wong (email: camilla.wong@utoronto.ca)
2. Bilkish Cassim (Email: cassimb@ukzn.ac.za)
3. Arjen Slooter (Email: A.Slooter-3@umcutrecht.nl)
4. John Joska (email: John.Joska@uct.ac.za)

All the authors have contributed to this work and agreed to its content. The study has received all the relevant ethics, provincial and governmental approvals.

Yours sincerely,

Jonathan Peter

D2. STARD checklist for reporting of diagnostic studies

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	6
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	7
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	7
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	7
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	7
Test methods	7	The reference standard and its rationale.	8
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	8
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	8
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	8
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	8
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	9
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	7
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	10
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	10/11
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	11
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	12
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	11,30
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	30
	22	How indeterminate results, missing data and outliers of the index tests were handled.	29
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	N/A
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	16-19

D3. Study clinical record forms

Form 2: Admission Data Capture Form

Patients Name:_____ Age/D.O.B: _____
Date of Admission:_____ Sex: M F
Date of Admission to G Floor:_____ Race: W B C O
Hospital folder # _____

Exclusion Criteria (Circle)
Coma (GCS<12) Aphasia ICU admission Verbal consent refused

Pre-morbid functioning
ADLs (including dressing, feeding, bathing, grooming, and toileting) (Circle)
Independent Requires Assistance Permanent Nursing Care Institutionalised

Risk Factors for delirium	**Yes**	**No**
Age 80+		
Visual Impairment (6/12 at 6m)	▫	▫
Auditory Impairment (whisper at 1m)	▫	▫
Depression (previous diagnosed/meds)	▫	▫
Dementia (prior formal cog. testing)	▫	▫

Admission Details

Preadmission medications(tick) & dosage:

Diuretics	-
Amitriptyline	-
Opiates	-
Psychotropics	- (specify)
ARVS	- (list)
TB Rx	- (list)
Digoxin	-
NAIDS	- (list)
Anitbiotics	- (list)
Statins	-
Beta blockers	-
HRT	-
Warfarin	-
Other specify	-

Admission Vitals

Temp:___ BP:_____ HR:_____ VX:_____ RR: _____

No of diseased organ systems:_____

Blood Results:

Hb:_____ WCC:_____ Platelets:_____ CRP:_____

Na:_____ K:_____ Urea:_____ Creat:_____

ALT:_____ Total Bili:_____ Ca^{2+}:_____ Mg^{2+}:_____

PO_4:_____ pO_2:_____ Sats:_____

HIV status: positive negative unknown Tested: Yes No Refused

Latest CD_4 count: _____ Date: _____

HAART: Y N If Yes, Specify drugs & Dose _____

Previous TB: Y N Date: _____ Completed 6/12 Rx Y N

Form 3a: Initial AMT & Assessment

Patient Name _____
Patient folder # _____

Date and Time of testing _____

Verbal consent taken Y N

Abbreviated Mental Test Score

1) What is your age? (+ 5 years) /1
2) What is the time? (Nearest hour, or a.m. / p.m.) /1
3) Address for recall at the end of test: 42 Strand street /1
4) What is the year? /1
5) What is the name of this place? (GSH) /1
6) Recognition of two persons (i.e. doctor, nurse) /1
7) Date of birth (month and year) /1
8) Date of Christmas /1
9) Name of current South African president /1
10) Count backwards from number 20 to number 1 /1

TOTAL /10

Communication barriers present at the time of testing: (Circle)

Deafness Depression Dysphonia Language barrier

After testing folder assessment

Notes about delirium appear in the hospital folder? (Circle) Y N

Formal Cognitive Testing done & recorded: Y N (If Yes, specify_____)

Date test to be repeated: _____

Name/Signature of Investigator:

Form 3b: Follow-up AMT & Assessment

Patient Name _____

Patient folder # _____

Date and Time of Testing _____

Date of Previous Testing _____

No of previous Testings _____

Latest Vitals: Temp(in last 72hrs)_____ BP:_____ HR:_____ VX:___

RR: ___

No of diseased organ systems: _____

Latest Blood Results (Only if different from admission):

Hb:_____ WCC:_____ Platelets:_____ CRP:_____

Na:_____ K:_____ Urea:_____ Creat:_____

ALT:_____ Total Bili:_____ Ca^{2+}:_____ Mg^{2+}:_____

PO_4:_____ pO_2:_____ Sats:_____

CD4: (now available) _____

Incident risk factors

Physical restraints Y N

New medications added during hospitalisation & dosages: _____

Urinary catheter Y N

Delirium preventative devices present(e.g. clocks, lighting, newspapers) Y N

Abbreviated Mental Test Score

1) What is your age? (+ 5 years) /1
2) What is the time? (Nearest hour, or a.m. / p.m.) /1
3) Address for recall at the end of test: 42 Strand street /1
4) What is the year? /1
5) What is the name of this place? (GSH) /1
6) Recognition of two persons (i.e. doctor, nurse) /1
7) Date of birth (month and year) /1
8) Date of Christmas /1
9) Name of current South African president /1
10) Count backwards from number 20 to number 1 /1

TOTAL: /10

Communication barriers present at the time of testing: (Circle)

Deafness Depression Dysphonia Language barrier

Name/Signature of Investigator:

Form 4: Reference delirium testing

Patient Name _____

Patient Folder # _____

Date and Time of assessment _____

Patient education level _____

Translator required _____

Other barriers to testing _____

MMSE performed (separate form attached) Yes No

MMSE score /30

CAM performed Yes No

CAM assessment (separate form attached) Delirium diagnosed Yes No

Overall assessment (Interview, testing and DSM-IV) Delirium Yes No

Name of investigator: _____

Signature: _____

Form 5:Final Patient Outcome

Patient Name _____

Patient Folder # _____

Date of admission _____

Date of Discharge _____

Number of days in hospital: _____

Outcome: (Circle)

Death

Discharged to:

Step-down hospital (specify _____)

Family-dependant (requires help with Adls) Y N

Family/home independent

D4. Reference diagnosis and training materials

DSM-IV Criteria for Delirium

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
___yes___no

B. Achangeincognitionorthedevelopmentofaperceptualdisturbancethatisnotbetter accounted for by a preexisting, established or evolving dementia.
___yes___no

C. Thedisturbancedevelopsoverashortperiodoftime(usuallyhourstodays)andtendsto fluctuate during the course of the day
___yes___no

D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.
___yes___no

Adapted from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000. Copyright © 2000, American Psychiatric Association.

Confusion Assessment method training manual and coding guide used

Downloadable from:
www.hospitalelderlifeprogram.org/pdf/TheConfusionAssessmentMethod.pdf

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20 November 2008

REC REF: 461/2008

Dr JG Peter
Department of Medicine

Dear Dr Peter

PROTOCOL: THE PREVALENCE, INCIDENCE AND ASSESSMENT OF DELIRIUM IN A TERTIARY SOUTH AFRICAN HOSPITAL WITH A HIGH HIV PREVALENCE.

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th November 2009.

Please submit an annual progress report if the research continues beyond the expiry date. Please submit a brief summary of findings if you complete the study within the approval period so that we can close our file.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

lemjedi

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

BMJ Instructions for authors

Editorial policies

BMJ Open is an open access journal dedicated exclusively to publishing medical research. The journal aims to provide rapid publication of research across a range of medicaldisciplines and therapeutic areas, through a continuous publication model. As well as publishing definitive articles, including small and lower impact studies, *BMJ Open* will publish study pre-protocols, protocols and pilot studies.

Submissions should be made through our online submission system (Scholar One Manuscripts). Submissions will only be published after peer review, and research protocols and reviewers' comments will be published alongside accepted manuscripts.

Articles should not be under review, or submitted for review, with any other journal when submitted to *BMJ Open*. This includes other BMJ Group journals.

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Article processing charges
BMJ Open levies an article processing charge that reflects the true cost of the services provided. The charge (exclusive of VAT for UK and EU authors) is: £1200. Charges for publishing a study protocol are 50% of the research article charge; a 50% discount will then also be available to the protocol's authors to publish the subsequent research findings in the journal, provided the results are submitted within a reasonable time from completion of the research. There are no submission or page charges, and no colour charges. There is a £50 surcharge for invoicing authors; unless a waiver has been granted, accepted articles will not be published until payment has been received.

Articles are published online approximately 30 days from processing to production. BMJ Group are unable to process, cancellations, refunds or returns for open access charges.

Waivers and discounts
We appreciate that some authors do not have access to funding to cover publication costs. The journal will accept part payment where only limited funds are available, and offers a waiver to authors unable to pay on request. No payment information is requested before an article is accepted, so the ability to pay cannot affect editorial decisions. *BMJ Open* offers a 100% waiver to corresponding authors from institutions based in Hinari Band 1 countries, and a 50% waiver to authors from institutions based in Hinari Band 2 countries. In recognition of reviewers' support, any reviewer that returns a full review, on time, can receive a 25% discount on article processing charges for a paper for which they are the corresponding author, if submitted within 12 months of completing the review.

Submission policies

All articles will be subject to the BMJ Group's high standards of ethics and transparency. See the following links for general BMJ Group policies.

Manuscript formatting
Editorial policies
Patient consent forms
Licence forms

Please note that in some cases *BMJ Open* has different submission requirements (e.g. there are no colour charges); where this is the case these are outlined below.

Article types

Research articles
All articles should include the following.

- The article title should include the study type.
- A structured abstract (max. 300 words) including the following (please note that for RCTs there is a specific CONSORT extension for abstracts):
    - objectives: clear statement of main study aim and major hypothesis/research question
    - design: e.g. prospective, randomised, blinded, case control
    - setting: level of care e.g. primary, secondary; number of participating centres. Generalise; don't use the name of a specific centre, but give geographical location if important
    - participants: numbers entering and completing the study; sex and ethnic group if appropriate. Clear definitions of selection, entry and exclusion criteria
      interventions: what, how, when and how long (this can be deleted if there were no interventions)
    - primary and secondary outcome measures: planned (i.e. in the protocol) and those finally measured (if different, explain why)
    - results: main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks
    - conclusions: primary conclusions and their implications, suggest areas for further research if appropriate. Do not go beyond the data in the article
    - trial registration: registry and number (for clinical trials and, if available, for observational studies and systematic reviews)
- An 'Article summary' section consisting of three headings: 'Article focus' (up to three bullet points on the research questions or hypotheses addressed); 'Key messages' (up to three bullet points showing the key messages or significance of the study); and a 'Strengths and limitations of this study' section. This should be placed after the abstract.
- The original protocol for the study, where one exists.
- A funding statement, preferably worded as follows. Either: 'This work was supported by [name of funder] grant number [xxx]' or 'This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- A competing interests statement. See this advice from the BMJ on what to include.
- Articles should list each author's contribution individually at the end; this section may also include contributors who do not qualify as authors.
- Any checklist and flow diagram for the appropriate reporting statement, e.g. STROBE (see below).
- Any article that contains personal medical information about an identifiable living individual requires the patient's explicit consent before we can publish it. We will need the patient to sign

our consent form, which requires the patient to have read the article. This form is available in multiple languages.

- Please provide a data sharing statement such as: "Technical appendix, statistical code, and dataset available from the corresponding author at <email address or url>. Participants gave informed consent for data sharing [or ...consent was not obtained but the presented data are anonymised and risk of identification is low... or consent was not obtained but the potential benefits of sharing these data outweigh the potential harms because...]" Accession codes should be supplied where available. If there are no further data available, please use this wording: "No additional data available". During submission authors can choose to send supplementary or underlying data to the Dryad repository, who will provide a permanent, citable and open access home for the dataset.

We recommend your article does not exceed 4000 words, with up to five figures and tables. Exceeding this will impact upon the paper's 'readability'. Supplementary and raw data can be placed online alongside the article, and we may request that you separate out some material into supplementary data files to make the main manuscript clearer for readers.

We also recommend, but do not insist, that the discussion section is no longer than five paragraphs and follows this overall structure (you do not need to use these as subheadings): a statement of the principal findings; strengths and weaknesses of the study; strengths and weaknesses in relation to other studies, discussing important differences in results; the meaning of the study: possible explanations and implications for clinicians and policymakers; and unanswered questions and future research.

Authors are encouraged to submit figures and images in colour - there are no colour charges.

At upload you will be asked to choose one general subject area that applies to your article - it will be published under this banner on the main table of contents. You will also be asked to select further subject headings to be used for the 'Browse by topic' section, and specific keywords for help with identifying reviewers.

Reporting guidelines
The guidelines listed below should be followed where appropriate. Please use these guidelines to structure your article. Completed applicable checklists, structured abstracts and flow diagrams should be uploaded with your submission; these will be published alongside the final version of your paper.

- CONSORT Statement (for reporting of randomised controlled trials: please use the appropriate extension to the CONSORT statement, including the extension for writing abstracts)
- STARD (for reporting of diagnostic accuracy studies)
- STROBE(for reporting of observational studies in epidemiology)
    - Checklist for cohort, case-control, and cross-sectional studies (combined)
    - Checklist for cohort studies
    - Checklist for case-control studies
    - Checklist for cross-sectional studies
- PRISMA (for reporting of systematic reviews)
- MOOSE (for reporting of meta-analyses of observational studies)
- STREGA (for reporting of gene-disease association studies)

The Equator Network (Enhancing the Quality and Transparency Of health Research) provides a comprehensive list of reporting guidelines.

Data sharing
See also our data sharing FAQs.

Study protocols
Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by

providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occur during the conduct of the study. Various resources exist that list the ingredients of an authoritative trial protocol, e.g. the UK Dept of Health/Medical Research Council Clinical Trials Toolkit and the US National Institutes for Health provide advice on how to structure a trial protocol. The SPIRIT (Standard Protocol Items for Randomized Trials) statement will be available soon (see here for details). It is an evidence-based tool developed through systematic review of a wide range of resources and consensus. It closely mirrors the CONSORT statement and also reflects important ethics considerations. BMJ Open will consider for publication protocols for any study design, including observational studies and systematic reviews. We strongly encourage you to register your study with a registry such as www.clinicaltrials.gov (this registration is mandatory for any clinical trial) or Prospero for systematic reviews. General BMJ Group policies apply (see above) on manuscript formatting, editorial policies, licence forms and patient consent (where applicable to study designs). Protocols should include, as a minimum, the following items.

- Protocol papers should report planned or ongoing studies. Articles that report results should be submitted as research articles.
- Title: this should include the specific study type, e.g. randomised controlled trial.
- Abstract: this should be structured with the following sections. Introduction; Methods and analysis; Ethics and dissemination. Registration details should be included as a final section, if appropriate.
- Introduction: explain the rationale for the study and what evidence gap it may fill. Appropriate previous literature should be referenced, including relevant systematic reviews.
- Methods and analysis: provide a full description of the study design, including the following. How the sample will be selected; interventions to be measured; the sample size calculation (drawing on previous literature) with an estimate of how many participants will be needed for the primary outcome to be statistically, clinically and/or politically significant; what outcomes will be measured, when and how; a data analysis plan.
- Ethics and dissemination: ethical and safety considerations and any dissemination plan (publications, data deposition and curation) should be covered here.
- Full references.
- Authors' contributions: state how each author was involved in writing the protocol.
- Funding statement: preferably worded as follows. Either: 'This work was supported by [name of funder] grant number [xxx]' or 'This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors'.
- Competing interests statement.

Study 'pre-protocols'
The journal will also be glad to consider publishing 'pre-protocols'; articles discussing provisional study designs that have yet to reach the stage of a formal proposal. These pre-protocols should include as much of the information required to publish a full protocol as possible, along with a statement of any areas of the study design where authors would particularly welcome comment. The pre-protocol will then be published online for community comment.

Pre-protocols should be presented formally. They should not be 'pitches' and should not discuss undeveloped research questions.

Pre-protocols will be peer-reviewed; reviewers will be checking that the research question and rationale are scientifically credible and ethically sound. They will be asked to consider the rest of the pre-protocol as it stands and comment on strengths and weaknesses.

Based on the reviewers' comments the pre-protocol will then be accepted for publication or declined. There will be no revision procedure. Reviewers' comments will be published alongside the submission.

Pilot studies
Articles reporting pilot studies should explain the work's wider context and explain why the term 'pilot

study' applies. The term 'pilot study' should not be applied to justify reporting a small-scale study. Justifications for a pilot study include:

- trialling a new procedure intended for use in a larger programme of research
- establishing power calculations required for a full-scale study
- establishing how many patients and/or healthcare professionals can be recruited
- evaluating the financial, technical, administrative or logistic feasibility of a full-scale study, including issues of data collection, protocol adherence, and questionnaire design.

The sample/patient size should still be justified. The article should explain the impact that the pilot study had on decisions regarding future research.

Rapid responses and online comments
We encourage readers to comment on articles published in *BMJ Open*. Please follow our guidelines set out in our Blog and eLetter response terms and requirements, available here. It is also possible to post less-formal comments online at the end of articles using the Disqus commenting facility.

Peer review process

All articles published in *BMJ Open* will have been sent for external, open peer review. Reviewers will not be asked to judge for importance or breadth of appeal. Readers will be able to make these judgements for themselves. We recommend you use our instructions for reviewers as a checklist to ensure that your article is complete. Upon publication, all previous versions of the manuscript will also be made available, as will the reviewers' comments and authors' replies to those comments.

Peer review of study protocols
BMJ Open will consider publishing without peer review protocols that have formal ethical approval *and* funding from a recognised, open access advocating research-funding body (as listed by the JULIET project). Please provide proof that these criteria are met when uploading your protocol. Any protocols that do not meet both these criteria will be sent for open external peer review, with reviewer comments published online upon acceptance, as with research articles. Reviewers will be instructed to review for clarity and sufficient detail. The intention of peer review is not to alter the study design. Reviewers will be instructed to check that the study is scientifically credible and ethically sound in its scope and methods, and that there is sufficient detail to instil confidence that the study will be conducted and analysed properly.

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Supplements

The BMJ Group journals are willing to consider publishing supplements. Supplement proposals may be made at the request of:

1. The journal editor, an editorial board member or a learned society may wish to organise a meeting, sponsorship may be sought and the proceedings published as a supplement.
2. The journal editor, editorial board member or learned society may wish to commission a supplement on a particular theme or topic. Again, sponsorship may be sought.
3. The BMJ Group itself may have proposals for supplements where sponsorship may be necessary.
4. A sponsoring organisation, often a pharmaceutical company or a charitable foundation, that wishes to arrange a meeting, the proceedings of which will be published as a supplement.

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